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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/518,501	Applicant(s) ERION ET AL.	
	Examiner Thomas McKenzie Ph.D.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20-46,48-153,155-157,161 and 163-173* is/are pending in the application.

4a) Of the above claim(s) *58-149,161,163,164 and 167-170* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,20-46,48-57,150-153,155-157,165,166 and 171-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7&11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 2/25/02. There are one hundred sixty-nine claims pending and sixty-seven are under consideration. Claims 1-16, 17-46, 48-57, 165, and 171-173 are compound claims. Claims 150-153, 155-157 and 166 are method of preparation claims. Applicants have amended claims 1-3, 38, 42, 46, 48, 50, 150, 151, 155, 161, and 163-165. Claims 166-173 are new. Applicants have cancelled claims 19, 47, and 154. Claims 166-173 are new. This is the second action on the merits. The application concerns some cyclic phosphate amides and preparations thereof.

Response to Amendments

2. Applicants amendment to the claims specifying that only one Y may be nitrogen and the other oxygen, overcomes the improper Markush rejection made in point #3. The references described in point #4 in IDS #7 have been received along with a new PTO-1449. Both have been signed and are included. Applicants' argument that the HY-CH(V)CH(Z)-CW(W")-YH includes compounds with W = Z =hydrogen and V = W' with the meso configuration is persuasive. These compounds will be exclude by Applicants' proviso "is chiral". This, the objection made in point #5 is withdrawn. Applicants point to the figure at the top of page 17 to indicated what they intend by "beta and gamma position" fusion. Thus, the indefiniteness rejection made in point #6 is withdrawn. Applicants point to their

definition of "acyl" in line 1, page 12 of the specification. Thus, the indefiniteness rejection made in point #7 is withdrawn. Applicants' clarification that TS means thymidylate synthase overcomes the indefiniteness rejection made in point #11. Applicants point to the list spanning pages 22-23 defining the abbreviations used in the claims. Thus, the indefiniteness rejection made in point #12 is withdrawn. Applicants' amendment to claims 38, 42, 46, and 165 replacing "prodrug" by "compound" overcomes the indefiniteness rejection mad in point #13.

Applicants clarify that the "chiral alcohol" of claim 156 is a reagent which is incorporated into the final cyclic phosphoramidite and is not a catalyst or auxiliary. That is, the chiral alcohol is a molecule HO-CH(V)CH(Z)-CW(W")-NH_2. The compound of formula I, recited in claim 166 must be chiral because it is made from this alcohol. Thus , the indefiniteness and utility rejections made in point #16 are withdrawn. Applicants' argument concerning the proviso that two of the substituents on the phosphorus-containing ring may not be hydrogen or alkyl is persuasive. Thus, the anticipation rejections made in points #19-21, 23, and 25 are withdrawn. Applicants' argument that benzo fused phosphorus-containing rings, lacking hydrogen atoms at the bridgehead are excluded by formula I, which has hydrogen atoms at the carbons bearing substituents V and Z, is persuasive. Thus, the anticipation rejections made in points #22 and #24 are withdrawn.

Election/Restrictions

3. Newly submitted claims 167-170 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: synthesis claims 167-170 belong to non-elected group XX of the initial restriction. Compound claim 170 belongs to non-elected Group XXII of that restriction. Synthesis claim 166 belongs to a third method of synthesis, distinct from both Groups XIX and XX of the original restriction. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 167-170 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. This application contains claims 58-149, 161, 164, 165, and 167-170 drawn to an invention nonelected without traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. Applicants have requested rejoinder of all their sixteen distinct groups of use claims. Applicants argue that no serious burden exists on the Examiner for the additional use claims. This is not persuasive. The separate uses are clearly distinct

inventions and Applicants made no argument regarding this issue. The distinct uses raise separate issues of enablement, written description, and indefiniteness. Thus, a serious burden is created.

Rule 141(b) refers to a process of making and a process of use in the singular. Applicants did not file under rule 371, but PCT Rule 13.2 is unequivocal. Only one process of making and one process of using may be contained in any International Application. According to the MPEP §1850 C: "Combinations of Different Categories of Claims. The method for determining unity of invention under PCT Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application: (A) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product". Understandably, there is little case law concerning this issue. However the Commissioner of Patents wrote *In re Caterpillar Tractor Co.* 226 USPQ 625 that "[t]he above language makes clear that Rule 141, as amended in response to U.S. adherence to the PCT, does not restrict or hinder established U.S. practice. The language also makes clear that the unity of invention rules under the PCT are, as Dr. Bogsch said (Pet. Ex. 80, p. 19), "very near to the American rules."" This

decision was overturned by the U.S. District Court Eastern District of Virginia on an issue of restriction of apparatus, which might be used for other processes. However, Judge Bryan, did not rule on the number of such distinct apparatus claims or on the convergence of PCT and US practice.

Claim Rejections - 35 USC § 112

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-3, 7, 9-18, 20-46, 48-53, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in lines 16-17, page 128, "M is selected from ... but is not an FBPase inhibitor" is indefinite. What do Applicants intend by "biologically active agent? How active and active as what?

7. Claims 1-3, 7, 9-18, 20-46, 48-53, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in lines 20-21, page 128 "M is not -NH(lower alkyl), -N(lower alkyl)$_2$" is indefinite. M-PO_3^{-2} etc must be biologically active. Are $^{-2}O_3P$-NH(lower alkyl) or $^{-2}O_3P$-

N(lower alkyl)$_2$ biologically active? If not, the proviso excluded something that is not present.

These two rejections will be considered together. Applicants clarify that FNBase is fructose 1,6-bisphospahease. Applicants point to the paragraph spanning pages 21 and 22 to clarify the nature of the radical M. This passage implies that M-PO_3^{-2} etc must be the biologically active agent. The radical M itself might contain phosphorus but it would be a second phosphorus atom. The compound M-H might or might not be biologically active. However, we do not know if only therapeutic activity is indented. Are poisons and biochemical intermediates also covered by the term?

Still uncertain is the structure of the radical M. Search of the US Patent file for phrases containing the terms "group" "attached" "PO_3^{-2}", and "biologically active agent" reveals only two occurrences in PreGrant Publication 20020052345 and US Patent 6,312,662 both by Applicants. Search on the Internet is also unfruitful. Applicants have not asserted that it is an art-recognized phrase and the Examiner can find no evidence that is so recognized.

The proviso concerning amines only clouds the issue. The Examiner does understand what radicals are excluded and that it was done to avoid art. Applicants' uncertainly about the amine exclusion means that they also are

uncertain as to the metes and bounds of the structure of M if they are uncertain about the biological activity of $^{-2}O_3P$-NH(lower alkyl).

8. Claims 1-18, 20-46, 48-57, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 23, page 128 and elsewhere, Applicants claim "prodrug". The word "prodrug" is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug"

Applicants clarify that they are indeed, claiming prodrugs of the prodrugs of formula (I). They point to lines 7-28, page 15 to clarify what they intend by "prodrug". This is not persuasive for three reasons. Firstly, the passage uses open language "include but are not limited". Secondly, the passage says that "standard prodrugs" are intended. Yet, Wolff (Burger's Medicinal Chemistry) in section 9.1 makes clear that design of prodrugs is an empirical exercise and no standard recipe

exists, "may then be possible to identify the means by which the difficulties can be overcome". Thirdly, we know what the concept of prodrug entails. What we do not know is what specific compounds Applicants claim.

9. Claim 150 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 150 provides for transforming "a compound drug having a $-PO_3^{2-}$ ...", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. All the word "transforming" does is delineate which molecules are staring materials and which are products. What chemical reactions are being claimed?

Claim 150 remains rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Applicants appear to be agreeing with the Examiner that no steps are indicated in the claimed process. While the process may consist of a single step, how is the enablement and written support for the claim to be determined if we do not know of what the process consists? How is the public to understand the metes and bounds of the claim?

10. Claims 155-157 remain rejected and claim 166 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "oxidizing agent" is indefinite. Pauling's "General Chemistry" on page 248 says, "[a]n atom, molecule, or ion which takes up electrons is called an oxidizing agent". "The Condensed Chemical Dictionary" defines "oxidizing material" as "any compound that spontaneously evolves oxygen..". What are the structures of the reagents, whose use Applicants claim? The Examiner suggests using lines 16-18, page 93 to list the "oxidizing agents" intended.

Applicants argue that the role of the oxidizing agent is clear in that a phosphorus atom is to be oxidized to the +5 oxidation state. This is true but not persuasive. Applicants are listing the function the reagent is to perform but not the structure of the reagents whose use is claimed. Attempting to define structure by function is not proper when the structures can be clearly expressed in terms that are

more precise. It is not sufficient to define a chemical structure solely by a single chemical property.

11. Claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrase in lines 16-17, page 128, "M is selected from ... but is not an FBPase inhibitor" lacks written description. Applicants' claims are drawn to any radical derived from a molecule with a certain functional group and with a general biological property. What are the structures of these molecules? Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-157, 165, 166, and 171-173. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. Applicants' dependant claims, listing the specific diseases treated, do not clarify what chemical radicals are intended here.

Applicants correctly argue that only a portion of formula I is claimed in functional terms. They also point out that some structural guidance is the provided

to the identity of M, namely that when it is attached to a phosphorus atom, the resulting molecule be biologically active. They also look to the recently promulgated USPTO Written Description Guidelines for direction. The guidelines have been incorporated into the MPEP § 2163, Section A, which says in part, "However, as discussed in paragraph I., supra, the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art" and "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function." "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

The radical M is an essential feature. The question then, is, would the skilled medicinal chemist understand from the phrase in question, what radicals M were intended. The discussion above concerning the indefiniteness of this phrase means that they would not. Applicants' exclusions of alkyl amines from the list of claimed M groups means that they do not understand the phrase.

12. Claims 1-18, 20-46, 48-57, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must be even more unclear.

Applicants argue that preparation of prodrugs is standard in the art of medicinal chemistry and cite two references, one twenty-five years old and the other twenty-seven years old. On this basis, they assert that the skilled medicinal chemist would not only know what compounds are prodrugs but also how to make them.

This is not persuasive for four reasons. Firstly, the specification provides no structural guidance and defines "prodrug" in purely functional terms. We know what the concept of prodrug entails. What we do not know is what specific compounds Applicants claim. Secondly, none of the citations is of record or

accessible to the Examiner. Thirdly, none of the references teaches how to make prodrugs of Applicants compounds or even of compounds closely related by structure to Applicants'. Fourthly, finding a prodrug is a largely empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty.

For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting passes the threshold of undue experimentation.

Wolff (Burger's Medicinal Chemistry) in section 9.1 outlines the research program that must be undertaking to prepare a prodrugs including collaboration between the skilled medicinal chemists and metabolism specialists. Banker (Modern Pharmaceutics) says on page 451, first paragraph that "preparation of prodrugs is becoming a common practice", implying that it is not routine as of 1996. Banker (Modern Pharmaceutics) says on page 596, third paragraph that "extensive development must be undertaken to find the correct chemical modification". Clearly an invitation to open-ended and potentially inconclusive research.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

RICHARD RAWLINGS
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TCMcK
July 12, 2002

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